I. SULFONATE SALTS OF SUBSTITUTED BENZIMIDAZOLES

II. REDUCTION OF NITRO CARBOXYLIC ESTERS

BY

KARL MAURICE BECK

B. S., Monmouth College, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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PART ONE

SULFONATE SALTS OF SUBSTITUTED BENZIMIDAZOLES

Introduction

In the course of the search during the war for compounds with antimalarial activity, several "sulfa" type compounds were prepared. The compound 2-metanilamido-5-chloropyrimidine, commonly called "metachloridine," had sufficient activity to arouse interest in other pyrimidines and in the structurally analogous benzimidazoles, particularly 2-metanilamido-benzimidazole and its 5-chloro derivative.

A generally satisfactory method of synthesis of sulfonamide type compounds from the combination of the amine and the sulfonyl chloride in pyridine gave anomalous results when applied to the 2-aminobenzimidazoles. A salt structure for the product from the reaction of 2-aminobenzimidazole with N-acetylsulfanilyl chloride was suggested by Price and Reitsema (1).

This work was undertaken to confirm this salt structure and to determine when salts were formed by this method by checking structures of other "sulfa" compounds synthesized on the antimalarial research program and reported in the literature.

Discussion of Results

It has been found that sulfonate salts of 2-aminobenzimidazoles can be made by direct combination of aqueous solutions of the sulfonic acid and of the 2-aminobenzimidazole derivative. The "sulfabenzimidazole" of Raiziss, Clemmence, and Freifelder (2) was shown to be 2-aminobenzimidazole sulfanilate by the synthesis of the compound by this method. Salt structures of 2-aminobenzimidazole *m*-nitrobenzene-

sulfonate and 2-aminobenzimidazole metanilate, prepared by Price and Reitsema (1) by indirect methods, were confirmed by the synthesis of both of these compounds by this direct method.

2-Amino-5-chlorobenzimidazole was established as the product of the reaction of *p*-chloro-*o*-phenylenediamine with cyanogen bromide (3) by direct chlorination of 2-aminobenzimidazole to give the same compound. The *m*-nitrobenzenesulfonate of this 2-aminobenzimidazole derivative was prepared.

The *bis*-*p*-nitrobenzenesulfonate of 2-amino-4,6-dimethylpyrimidine was prepared from 2-amino-4,6-dimethylpyrimidine and *p*-nitrobenzenesulfonic acid, but it was found that the 2-aminopyrimidines in general form sulfonate salts with difficulty or not at all.

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PART TWO

REDUCTION OF NITRO CARBOXYLIC ESTERS

Introduction

Recently Leonard, Hruda, and Long (1) developed a practical synthesis of pyrrolizidines by the reductive cyclization of γ-nitroesters. Since the γ-nitroesters can be prepared by Bruson's (2) method of 1,4-addition of nitroparaffins to acrylic esters, it seemed feasible to extend this synthesis of heterocyclic nitrogen compounds by the reduction of representative nitro carboxylic esters. This research was under-

taken to prepare other pyrrolizidines and to try to extend the method to the synthesis of the monocyclic pyrrolidines.

Since a series of 8-alkylpyrrolizidines was made available through this research, it was also of interest to determine the basicities of these compounds, in order to compare their basic strengths with known values for other heterocyclic amines and to determine the effect on basicity of an alkyl side-chain of sufficient length to cover either partially or totally the face of the nitrogen atom.

Discussion of Results

Bruson's (2) method of condensation of nitroparaffins with acrylate esters in the presence of a strong basic catalyst was extended to the synthesis of methyl γ-nitroheptanoate and dimethyl γ-*n*-propyl-γ-nitropimelate from 1-nitrobutane and methyl acrylate, and of methyl γ-nitro-*iso*-heptanoate and dimethyl γ-*iso*propyl-γ-nitropimelate from nitro-*iso*butane and methyl acrylate.

The formation of *tris*-(2-carbomethoxyethyl)-nitromethane in the condensation of nitromethane with methyl acrylate was proved conclusively by conversion of sixty-five per cent of the crude, non-distillable reaction product to *tris*-(2-carboxyethyl)-nitromethane.

The reductive cyclization of γ-nitro carboxylic esters to form nitrogen heterocyclic compounds was extended to the synthesis of 8-*n*-propylpyrrolizidine from dimethyl γ-*n*-propyl-γ-nitropimelate, 8-*iso*propylpyrrolizidine from dimethyl γ-*iso*-propyl-γ-nitropimelate, and 1,2-diethylpyrrolidine from ethyl γ-nitrocaproate and ethanol. Dioxane was found to be the best solvent for the reduction of γ-alkyl-γ-nitropimelates to pyrrolizidines, and it was found that pyrrolidines formed from the reduction of γ-nitro monocarboxylic esters in ethanol could best be separated from the solvent and the water formed in the reaction by addition of benzene and removal of the low-boiling benzene-ethanol-water azeotrope. The reductive cyclization did not proceed satisfactorily in attempts

to prepare the following: 1-methyl-2-ethylpyrrolidine from ethyl γ-nitrocaproate and methanol, 2-methylpyrrolidine from ethyl γ-nitrovalerate, and 8-(γ-hydroxypropyl)-pyrrolizidine from crude *tris*-(2-carbomethoxyethyl)-nitromethane.

The basic strength constants of 2-methylpyrrolizidine, 8-methylpyrrolizidine, 8-ethylpyrrolizidine, 8-*n*-propylpyrrolizidine, 8-*iso*propylpyrrolizidine, and 1,2-diethylpyrrolidine were determined, using the method employed by Adams and Mahan (3) for other heterocyclic amines. The 8-alkylpyrrolizidines were found to be more basic than 2-methylpyrrolizidine, apparently because of the increased inductive effect of the alkyl group in closer proximity to the nitrogen atom. All the pyrrolizidines were more basic than 1,2-diethylpyrrolidine, illustrating that the bicyclic bases are much stronger than analogous monocyclic bases with the same number of carbon atoms and the same mode of attachment, due to the steric effect on basic strength of "tying back" the alkyl groups. The basic strength constants of 8-methyl-, 8-ethyl-, and 8-*iso*propyl-pyrrolizidine were very close, indicating that the "polar effect" and the "steric effect," both of which increase from methyl to ethyl to *iso*propyl, are about equal in influence on the basicity and are operating in opposite directions. The basicity of 8-*n*-propylpyrrolizidine was much less than that of the other 8-alkylpyrrolizidines, demonstrating the predominance of the greatly increased steric effect over the slightly increased inductive effect of the longer chain. The order of decreasing basicity of 8-methylpyrrolizidine > 8-ethylpyrrolizidine > 8-*n*-propylpyrrolizidine follows the order of increasing steric hindrance of the alkyl groups.

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VITA

The author was born in Belleville, Illinois, on June 16, 1922. He attended public schools there and in Springfield, Illinois, and was graduated from Springfield High School in May, 1940. In September, 1940, he entered Monmouth College, and he received his Bachelor of Science degree from that school in August, 1943. After one semester of graduate study at the University of Illinois, during which he was a teaching assistant in inorganic chemistry, he began working full-time on a National Defense Research Committee contract under Dr. C. C. Price at the University in February, 1944. In June, 1944, he went to Bushnell, Florida, to work on Chemical Warfare under the same contract. In February, 1945, he returned to the University of Illinois to work full-time on an antimalarial research program sponsored by the Committee for Medical Research under Dr. Price. In February, 1946, the author resumed graduate study and held a part-time teaching assistantship in inorganic chemistry. From October, 1946, until February, 1948, he held a University fellowship.

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